6.8.1.6. A 200 mg Single Dose, Bioequivalence Study of Three Thalidomide Formulations: 50 mg Marketed Capsule, 50 mg New Capsule, and 200 mg New Capsule in Healthy Male and/or Female Volunteers (Thal/BE-01-001)

Celgene sponsored a single-dose, randomized, open-label, three-way crossover study to compare two new thalidomide formulations (50- and 200-mg capsules) with the 50-mg originally approved capsule following a single 200-mg dose administered in the fasting state. The purpose of the reformulation was to reduce the number of capsules needed for dosing by making higher strength, smaller capsules.

This study was performed between 26 July and 11 August 2001 at MDS Pharma Services in Phoenix, Arizona. The principal Investigator was Irving E. Weston, MD. The study was performed under Celgene's IND 48,177. Thirty healthy volunteers enrolled (26 males and 4 females). Subjects, primarily Caucasian (77%), had a mean age of 38 years (range 18 to 55 years). Twenty-three subjects (20 males and 3 females) completed the study according to protocol. One subject was discontinued when it was realized that he was dosed incorrectly according to the randomization. The Investigator discontinued 6 subjects due to abnormal laboratory test results that were clinically significant (WBC and bacteria in urine [2 subjects]; elevated creatine kinase [2 subjects], and 1 subject each with elevated BUN and ALT). Pharmacokinetic analysis was performed on all 30 subjects and statistical analysis was performed on data from the 23 subjects who completed the three study periods.

Treatment A (4 × 50 mg new capsules), Treatment B (1× 200 mg new capsule), and Treatment C (4 × 50 mg original capsules) were administered to each subject on three different occasions, separated by 7-day washout periods. After each oral administration, blood samples were obtained pre-dose and over a 24-hour period at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose. Samples were analyzed using LC/MS/MS at MDS Pharma Services in Lincoln, Nebraska.

Following administration of a single 200- mg dose using Celgene's new and original 50-mg capsule formulations, the peak plasma concentrations are reached by 4.1 and 3.9 hours, respectively, and the elimination half-lives are 7.9 and 6.1 hours, respectively. A comparison of Celgene's new 50-mg capsule formulation with the reference 50-mg capsule formulation and of the two test formulations (50- and 200-mg capsule strengths) indicates they are bioequivalent with regard to the rate and extent of absorption, according to criteria which require that the 90% confidence intervals for the comparisons of the ln-transformed C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-\infty)}$ be within the acceptable range of 80 to 125%.

The results of the comparison of the 50-mg capsule (administered as a single 200-mg dose) are summarized in In-text Table 6.36 below.

In-text Table 6.36
Summary of Mean Pharmacokinetic Parameter Values of Thalidomide for the New Formulation *vs.* the Original 50-mg Capsule Formulation Given as Single 200-mg Doses (4 × 50 mg Capsules)

Ln Transformed Parameter (Unit)	Mean Formulation		Statistical Comparison	
	New 50 mg (4 × 50 mg)	Original 50 mg (4 × 50 mg)	90% CI	% Mean Ratio
C_{max} (ng/mL)	7.415	7.540	8.25 – 95.5	88.8
$AUC_{(0-t)}$ (ng·hr/mL)	9.857	9.943	89.2 – 95.1	92.1
$AUC_{(0-\infty)}$ (ng·hr/mL)	10.01	10.03	93.8 – 101.9	97.8

A comparison of the two test formulations, the 50-mg and 200-mg capsules, is provided in the table below.

In-text Table 6.37
Summary of Mean Pharmacokinetic Parameter Values of Thalidomide for the New 50- and 200-mg Capsule Formulations Given as Single 200-mg Doses

Ln Transformed Parameter (Unit)	Mean Formulation		Statistical Comparison	
	New 50-mg (4 × 50 mg)	New 200-mg (1 × 200 mg)	90% CI	% Mean Ratio
C_{max} (ng/mL)	7.415	7.378	96.3 – 111.6	103.7
$AUC_{(0-t)}$ (ng·hr/mL)	9.857	9.847	98.1 – 104.6	101.3
$AUC_{(0-\infty)}$ (ng·hr/mL)	10.01	10.02	94.9 – 103.2	99.0

A direct comparison was made of the new 200 mg capsule formulation with the original 50-mg capsule formulation and was shown to be bioequivalent with regards to comparisons of the ln-transformed AUCs, but misses a strict interpretation of bioequivalence with a lower confidence interval of 79.5% rather than the required 80% for ln-transformed C_{max}. However, as the original capsule was replaced by the bioequivalent reformulated 50-mg capsule to which the new 200-mg capsule is bioequivalent with respect to both AUC and C_{max}, this comparison will not be further presented. For further discussion, please refer to the full study report.

6.8.2. Published Studies in Oncology Patients

No striking differences in pharmacokinetic parameter values were observed in cancer patients who received high doses of thalidomide. The only difference seen was in apparent volume of distribution and elimination half-life values seen in patients that received up to 1200 mg/day doses of thalidomide. These differences, however, could be attributed to fact that measurements were taken in an elderly patient population. The results of these studies are discussed in the text that follows.